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ORIGINAL ARTICLE

The effect of irbesartan in reducing cardiovascular risk in hypertensive type 2 diabetic patients: an observational study in 16 600 patients in primary care

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SUMMARY

Objectives: As arterial hypertension substantially increases the risk of premature death, cardiovascular disease and renal insufficiency in patients with type 2 diabetes, effective and safe antihypertensive therapy is of importance. Therefore, the effect of irbesartan as monotherapy, or in fixed combination with hydrochlorothiazide, on blood pressure, metabolic parameters and microalbuminuria and the safety and tolerability of the drug were assessed.

Research design and methods: Multicentric, prospective, open phase IV study over 3 months in 16 600 patients with the clinical diagnoses of hypertension and type 2 diabetes. Blood pressure was measured sphygmometrically and albuminuria was assessed with semi-quantitative urine dipsticks.

Main outcome measures: Systolic (SBP) and diastolic (DBP) blood pressure reduction, proportion of patients with microalbuminuria and cardiovascular risk calculated based on the SCORE score, each after a follow-up of 3 months compared to baseline. Number and nature of adverse events (AEs).

Results: The sample consisted of 51.3% men, mean age was 62.2 ± 10.7 years, 53.9% of patients were overweight and 26.4% were obese. Mean SBP/DBP decrease after 3 months was 22.3/11.2 mmHg. The BP lowering effect was similar in the analyses of various subgroups (according to age group, sex, presence of micro- or macrovascular complications). Irbesartan treatment reduced the percentage of patients with microalbuminuria from 45.6% to 30.6% at 3 months (32.9% relative reduction). Metabolic parameters (lipids, blood glucose, HbA1c) and weight were improved significantly or showed trends for improvement, respectively. The mean 10-year cardiovascular risk as calculated with the SCORE score was decreased from a baseline value of 9.8% to 5.7% (–58% relative reduction). Tolerability was excellent: only 0.3% experienced an AE.

Conclusions: Treatment with irbesartan in patients with concomitant hypertension and type 2 diabetes led to large blood pressure reductions. In view of the renoprotective effect documented by the reduced rate of patients with albuminuria, and the improvement of further metabolic parameters, these changes translate into a reduction of cardiovascular risk.

Introduction

Hypertension, defined as a blood pressure (BP) ≥ 140/90 mmHg, occurs in up to 75% of patients with type 2 diabetes[1]. The comorbid presentation of diabetes and hypertension is frequent and thus represents a substantial public health issue: In a recent cross-sectional study in primary care, it was diagnosed in 10.4% of men

and 8.6% of women. In 81% of cases, additional concomitant diseases or complications were found[2,3]. When occurring concomitantly, both diseases are multiplicative risk factors for sudden cardiac death, coronary heart disease, heart failure and peripheral arterial disease[4,5]. In hypertensive diabetics, the mortality risk is approximately 4 times higher than in patients without hypertension and diabetes. The WHO/ISH guidelines highlight the fact, that patients with the concomitant presentation carry 'high risk', irrespective of the grade of the diseases[6]. Notably, diabetic women have the same risk as their male peers, i.e., diabetes appears to obviate the protective effects of female sex hormones[7].

Several studies have impressively shown that antihypertensive therapy reduces the cardiovascular risk in hypertensive patients with diabetes to a greater extent than in patients with hypertension alone (HOT[8], STOP-2[9], UKPDS 38[10]). It must be stressed that BP lowering therapy is regarded as the most important intervention in diabetes[11]. It reduces the incidence of microvascular complications more than normalization of hyperglycemia[12,13] and, by the same token, leads to a substantial reduction of macrovascular complications and thus of premature mortality.

Despite this compelling indication, antihypertensive therapy is underutilized in hypertensive patients with diabetes: only a quarter of patients had normalized BP in the above primary care survey[14].

Angiotensin receptor antagonists (ARBs), such as irbesartan, are the first-line therapy in all major guidelines and are especially recommended in patients with diabetic nephropathy[15–17]. Irbesartan treatment may be especially useful, as it is currently not only approved for the treatment of hypertension, but also for the treatment of renal disease in patients with hypertension and diabetes[18]. The aim of the present study was to assess the antihypertensive and renoprotective efficacy and tolerability of irbesartan or irbesartan-based regimens in patients with hypertension and type 2 diabetes and its translation into cardiovascular risk reduction (SCORE).

Methods

Design

This was a 3-month, multicentre, open-label, single-arm, prospective, observational phase IV study, which was conducted by 1844 general physicians (GPs) throughout Germany. This specific study type is regulated in the German Drug Law (AMG) § 67(6) and is primarily intended to gather knowledge about the safety and efficacy of marketed drugs in daily practice. Importantly, the protocol did not stipulate any interventions or any changes in routine treatment. The procedures and decisions of the physicians were not influenced and they were completely free to select which patients to treat with the licensed drug under investigation, which diagnostic measurements they used and the way in which they controlled the course of treatment or which concurrent or additional medication they prescribed. Due to the non-interventional type of the study, no ethical approval nor patient informed consent were obtained in accordance with applicable local laws and regulations. The GPs collected data on the background characteristics of the patients and on key efficacy variables and adverse events (AEs) on case report forms (CRFs). If any serious adverse events (SAEs) occurred, the GPs were obliged to report them by completing a form within 24 hours and transmitting it to the manufacturer, who forwarded the report in a standardized format to the relevant authorities (Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn). The collected data, SAE forms and CRFs were not verified in comparison with the source data in the patient files, but the forms were routinely checked for plausibility and completeness. The federal panel doctors' association as well as the higher authorities were duly notified about this investigation. The participating GPs received a small compensation for the documentation of each patient, which is common practice for this type of study.

Patients and Study Conduct

The GPs selected patients with type 2 diabetes with concomitant arterial hypertension for once daily treatment with irbesartan 300 mg (Aprovel 300°) as monotherapy or as combination therapy with 12.5 mg hydrochlorothiazide (HCTZ) (CoAprovel 300°). The prescription of additional antihypertensive agents was allowed, if necessary. Patients with the irbesartan regimens were selected by the GPs, using a cohort approach. Only adult patients were to be included (≥ 18 years), but there were no additional exclusion criteria regarding concomitant medication or concomitant diseases. There were no stipulations regarding BP targets, however, German doctors to a considerable percentage follow the established guidelines of the German Hypertension League[19].

The parameters documented in the study included demographic characteristics (initials, age, sex, weight and height), medical diagnosis (type 2 diabetes and arterial hypertension with respective date of first diagnosis) and antihypertensive therapy within the

° Aprovel and CoAprovel are trade names of Sanofi-Synthelabo

Table 1. Baseline characteristics and concomitant diseases (n = 16600 evaluable patients)

Parameter	Value
Age (years) mean ± SD	62.2 ± 10.7
category < 40 (%; *n*)	2.2% (371)
category 40–65 (%; *n*)	58.2% (9613)
category > 65 (%; *n*)	39.6% (6541)
Height (cm) mean ± SD	170.6 ± 8.8
BMI (kg/m²) mean ± SD	28.2 ± 4.3
category < 19 (%; *n*)	0.3% (42)
category 19– < 25 (%; *n*)	19.5% (3195)
category 25– < 30 (%; *n*)	53.9% (8836)
category ≥ 30 (%; *n*)	26.4% (4320)
Risk factors at baseline (%)	
Family history of cardiovascular events	50.6%
Smoker	32.7%
Known diabetes	66.7%
Known hypertension	78.1%
Proteinuria	33.4%
Qualitative albumin status at baseline (%)	
Albumin positive	45.6%
Albumin negative	54.4%
Albumin/creatinine ratio	
negative/normal	36.9%
microalbuminuria	58.6%
macroalbuminuria	4.5%

BMI = Body mass index; SD = Standard deviation

previous 12 months (discontinued, with the reason for discontinuation, or ongoing). Blood pressure was to be taken as a mean of three sphygmomanometric measurements. If available from the charts, the following laboratory parameters were collected: creatinine, protein in urine, fasting blood glucose, HbA1c. Screening for microalbuminuria was performed with urine test strips at the discretion of the treating physician. For quantification of microalbuminuria, the categories negative, 10 mg/l, 30 mg/l, 80 mg/l and 150 ml/l were used and GPs were to tick the diagnoses microalbuminuria and proteinuria on the CRFs. Creatinine in urine was to be categorized as negative, 10 mg/dl, 50 mg/dl, 100 mg/dl, 200 mg/dl and 300 mg/dl. Urine dipstick tests were repeated after 3 months, as was documentation of antihypertensive treatment and weight. Blood pressure measurements were repeated and the laboratory parameters creatinine, protein in urine, fasting blood glucose, HbA1c were recorded, if available.

The following features of AEs were recorded if these occurred: description, first occurrence, grade of severity, outcome of events (recovered, recovered with sequelae, unresolved), likelihood of causal relationship (likely, probable, unlikely, no relationship).

Statistical Considerations

According to the predefined statistical analysis plan, the analysis was performed descriptively and was interpreted in an explorative way. Comparisons were done for blood pressure and proportions of patients with positive microalbuminuria tests between baseline and after 3 months. The absolute and relative frequencies of AEs and the efficacy and tolerability ratings were reported.

Post hoc analyses for subgroups defined by gender, BMI, diabetes duration, insulin treatment, strength of antihypertensive response, as well as previous and concomitant antihypertensive treatment, respectively, were carried out. Further predefined analyses were done according to risk groups, using the SCORE classification[20]. The following parameters were used for the calculation of this score: sex, age, total cholesterol (according to the Friedewald formula), systolic BP and smoking status. In the presence of diabetes, the score was increased by factor 2 with men and by factor 4 with women[20]. Calculations were done with and without the replacement of missing values. For total cholesterol and BP, the mean value of men or women was used; for missing smoking status 'non-smoking' was used. Risk groups were divided per quintiles.

The analysis of data was performed with the statistical software package SAS, version 8.2[21].

Regarding safety, the trial was adequately sized to identify rare AEs, i.e. those that may not have been detected in previous clinical studies (incidence 1:1000) with a probability of > 99.99% and very rare events (incidence 1:10000) with a probability of 81%.

Results

Baseline Characteristics

In the observational period between October 2002 and June 2003, a total of 17284 patients were documented, of which the data of 16600 could be used in the statistical analysis. Men and women were balanced [*n* = 8317 (51.3%) men, *n* = 7906 (48.7%) women], however, with higher age the proportion of women increased [> 65 years: 2884 (44.1%) men, *n* = 3492 (53.4%) women]. Mean age of patients was 62.2 ± 10.7 years; mean BMI was 28.2 ± 4.3 kg/m². The proportion of overweight individuals (BMI 25.0–29.9) was 53.9% and of obese individuals (BMI ≥ 30) was 26.4%.

Table 1 displays risk factors and laboratory values of patients at baseline. The proportions of smokers were somewhat higher in men (37.1%) than in women (28.1%), otherwise differences in the various items were small.

Table 2 summarizes the prevalence of concomitant diseases (in addition to diabetes and hypertension) at baseline. Only 31.3% of patients had no additional

Table 2. Concomitant diseases

Concomitant diseases	Prevalence (%)
Patients with concomitant diseases	68.7
Lipid disorders	45.9
Coronary artery disease	28.3
Peripheral arterial disease	16.9
Heart insufficiency	12.2
Neuropathy	11.9
Retinopathy	8.9
Stroke/TIA	7.3
Myocardial infarction	6.3
PTCA/stent	4.7
Bypass	3.4
Other disease	0.4

disease. Of all patients, 5142 (31%) had macrovascular complications only (coronary artery disease, stroke/transient ischemic attacks, peripheral arterial disease), 1015 (6%) had microvascular complications only and 1804 (11%) both macro- and microvascular complications.

At the beginning of the study, 38.1% of patients received irbesartan 300 mg as mono-therapy and 60.5% irbesartan 300 mg in combination with HCTZ 12.5 mg (in 1.4% treatment was not specified). Other irbesartan dosages were not used. On top of irbesartan with or without HCTZ, beta blockers were administered in 21.2%, calcium antagonists in 13.6%, ACE inhibitors in 3.4%, diuretics other than HCTZ in 6.9% and alpha$_1$-receptor blockers in 1.7%.

Blood Pressure Control

In comparison to baseline (159.6/93.1 mmHg), mean BP was decreased by 22.3/11.2 mmHg after 3 months. Regarding categorical responses, a decrease of > 20% in SBP/DBP compared to baseline was recorded in 19%/14% of patients, a decrease of > 10–20% in 46%/46% of patients. Only in 0.7%/2.2% was an increase of SBP/DBP noted. The BP lowering effect of irbesartan/HCTZ was similar in the analyses of the various subgroups (according to age group, sex, presence of micro- or macrovascular complications, SCORE quintiles; data not shown). Also, there were no differences between the full dataset and the dataset limited to patients with documented baseline and endpoint value.

Microalbuminuria

In the categorical analysis, almost every other patient (n = 5089 of 11 179 analyzed patients, 45.6%) had a positive dipstick test indicating microalbuminuria at baseline. At study end, this was the case for only n = 3422 (30.6%; absolute risk reduction: 15.0%). Only 69 previously negative patients had a positive dipstick test at study end. Of those 5098 patients who were dipstick positive at baseline, 1745 patients had a negative test at study end.

In the endpoint analysis, mean albumin decreased from 44.7 mg/l to 18.9 mg/l (median reduction: –20.0 mg/l). Albuminuria reduction was in the same magnitude in the different age groups and in men and women.

In the subgroup analyses of patients with micro- and macrovascular complications it emerged that patients without any of these complications had the lowest mean albumin value in their urine (36.1 ± 39.4 mg/l), while it was higher for patients with macrovascular complications only (41.8 ± 43.2 mg/l), for patients with microvascular complications only (50.0 ± 48.8 mg/dl) or those with both micro- and macrovascular complications (61.0 ± 60.6 mg/l), respectively. At study end, the latter groups with high average baseline values had the strongest albumin reduction. In the various SCORE groups, no important differences were noted for the baseline values or the changes, respectively.

Metabolic and Weight Changes

Table 3 summarizes changes in important metabolic and other parameters that are considered as risk factors or at least risk markers. All parameters were improved by study end.

Change of 10-year Cardiovascular Risk according to SCORE

The median 10-year cardiovascular risk was calculated according to the SCORE score in those patients ≤ 65 years (validation threshold for SCORE), for whom all necessary parameters for calculation were available. The distribution was skewed to the right (mean value higher than median) given the fact that many patients had a high risk. The mean risk was 9.8% (males 11.0%, females 8.5%) at baseline. After treatment with irbesartan, the mean absolute risk changed considerably by –4.1% (males –4.6%, females –3.5%) Table 4 summarizes the mean and median SCORE changes in men and women. Further post-hoc analyses in patients with BMI ≥ 30 kg/m² or BMI < 30 kg/m² and patients with and without microalbuminuria revealed similar results.

Safety and Tolerability

The rate of AEs was very low. Only 62 AEs were noted in 48 patients (0.3% of all patients). Two SAEs were noted (terminal renal insufficiency, not related to study medication; tremor, likely related). There were no deaths during the study.

Table 3. Changes in parameters between end of study and baseline

Parameter [Unit]	Baseline	Change from baseline Mean value ± SD [median]	Number of patients
Systolic blood pressure (mmHg)	159.6 ± 16.3	–22.3 ± 15.2 [–20.0]	15515
Diastolic blood pressure (mmHg)	93.1 ± 9.7	–11.2 ± 9.7 [–10.0]	15457
Heart rate (beats per minute)	76.7 ± 9.2	–3.7 ± 8.0 [–4.0]	14230
Body weight (kg)	82.1 ± 14.1	–1.0 ± 3.1 [–1.0]	16078
HDL cholesterol (mg/dl)	49.4 ± 19.3	1.9 ± 17.3 [2.0]	14009
LDL cholesterol (mg/dl)	147.0 ± 36.1	–12.1 ± 26.2 [–8.0]	14064
Triglycerides (mg/dl)	202.3 ± 79.3	–22.8 ± 55.0 [–15.0]	13896
Total cholesterol (mg/dl)	232.0 ± 39.9	–12.4 ± 30.0 [–8.6]	11688
Blood glucose (mg/dl)	149.8 ± 34.7	–25.5 ± 32.1 [–20.0]	15178
HbA_{1c} (%)	7.2 ± 1.0	–0.4 ± 0.7 [–0.3]	14214
		n (%)	
Albumin improved		1745 (15.6%)	11179
Albumin deteriorated		69 (0.6%)	
Albumin/creatinine ratio improved		265 (16.9%)	1568
Albumin/creatinine ratio deteriorated		86 (5.5%)	

Table 4. Changes in the SCORE 10-year risk at baseline and end of treatment

	Calculated 10-year cardiovascular risk (%)						
	Mean	SD	1% percentile[1]	25% percentile	Median percentile	75% percentile	99% percentile
Men (*n* = 2474)							
baseline	10.96	9.16	1.05	4.76	8.45	13.87	45.26
study end	6.32	4.75	0.65	2.95	5.26	8.20	23.75
difference	–4.64	5.77	–28.26	–5.81	–2.85	–1.29	1.57
Women (*n* = 2259)							
baseline	8.49	7.64	0.44	2.96	6.43	11.70	36.40
study end	5.00		0.27	1.80	3.97	7.14	20.06
difference	–3.49	4.68	–21.40	–4.62	–2.03	–0.79	1.21
Total (*n* = 4733)							
baseline	9.78	8.56	0.57	3.93	7.59	12.76	41.84
study end	5.69	4.58	0.36	2.38	4.67	7.68	22.21
difference	–4.09	5.31	–25.94	–5.24	–2.45	–1.03	1.31

SD = standard deviation. For the calculation of the 10-year cardiovascular risk the following parameters were used: sex, age, total cholesterol (according to Friedewald), systolic BP and smoking status. In the presence of diabetes, the score was increased by factor 2 with men and by factor 4 with women. The score was only calculated for patients for which all parameters were available at baseline and at study end (i.e., endpoint analysis without replacement of missing values). Patients above 65 years were excluded, as SCORE is validated only for patients below this threshold.

[1]Read the percentiles at baseline and at study end as follows, i.e. in line 1: 1% of patients had a 10 year risk of 1.05 or less, 25% a 10 year risk of 4.76 or less etc. The difference study end baseline is to be read as follows: 1% of patients had a 10 year risk reduction of 28.26% or less, 25% had a risk reduction of 5.81 or less, ..., 99% had a risk reduction or a risk increase of 1.57 (and 1% a risk increase of 1.58).

Discussion

In the present study, under daily practice conditions, irbesartan and irbesartan/HCTZ were shown to exert a profound BP lowering effect in patients with hypertension and diabetes. The BP decrease of –22/–11 mmHg (SBP/DBP) was in the same order as in another open phase IV study in a similar patient population and setting[22]. The size of both the diastolic and systolic BP lowering effect was substantial and would, in view of the well-known associations between BP levels and cardiovascular disease, be likely to translate into a substantial risk reduction. Results of the UKPDS showed that a decrease of 10 mmHg in mean SBP was associated with a 11–15% reduction in mortality related to diabetes, risk of myocardial infarction, risk of microvascular complications or any diabetes-related complications[23].

Interestingly, an improvement in all metabolic parameters was noted, which was small for the lipid changes, however, substantial for HbA1c. It is likely that these changes are due to the study circumstances that might improve patient compliance, but even so the thiazide component in those patients on combination therapy did not lead to untoward consequences. Notably, diuretics, at least in high doses, have been associated with untoward metabolic effects in the past and their use has been discouraged in susceptible populations such as patients with diabetes[24]. However, there is clear evidence from several endpoint studies, that thiazides are effective in reducing cardiovascular risk and mortality in diabetic hypertensive subjects[25]. Thus, this class has been included in the current recommendations for first-line treatment of diabetics, for example by the American Diabetes Association[1].

The capacity of irbesartan to reduce (micro-) albuminuria, as documented in this study, corresponds well to the findings of the Irbesartan Micro-Albuminuria (IRMA) in type-2 diabetes study, which showed that the progression of nephropathy can be substantially slowed by irbesartan treatment[26]. In the IRMA study, the restoration of normoalbuminuria after two years compared to baseline was 34% (95% confidence interval, 26–40%) in the irbesartan 300 mg group[26], while it was 53% (from 49% at baseline to 23%), for irbesartan based regimens in an open 6 month study in a similar setting[22]. Also patients with overt nephropathy benefit from irbesartan treatment as shown in the Irbesartan Diabetic Nephropathy Study (IDNT)[27].

An important aspect emerged when considering the total cardiovascular risk of patients using the SCORE score. As irbesartan-based treatment not only led to a substantially reduced blood pressure, but also has a favourable impact on further modifiable parameters relevant for the 10-year risk, the latter was decreased substantially. It is very important to realize that it is an estimate of the risk of fatal cardiovascular events and that the total cardiovascular risk would be two to three times higher than the figures quoted here[20]. The average total 4.1% 10-year risk reduction (from 9.8% at baseline) corresponds to a relative risk reduction of nearly a half (–42%). While it has to be proven, that this positive impact on risk factors, and thus total risk, can be maintained over the long term, the size of the effect is encouraging. It relates to the risk reductions seen in a large metaanalysis of prospective long-term studies, where an average, diastolic blood pressure reduction of about 10 mmHg translated into a reduction of cardiovascular risk of at least 37% and 56% less stroke[28].

Very few AEs were reported by the patients while on irbesartan alone or in combination with HCTZ. These data are in agreement with the well known tolerability of irbesartan as mono- or combination therapy, which resembles that of placebo[18].

The present results have to be considered against the background of several potential limitations. The study was not controlled and therefore the contribution of placebo effects is unknown. Second, in the absence of randomization procedures the influence of unknown biases, e.g. through patient selection, cannot be assessed. Third, the study duration was rather short in view of the life-long drug treatment antihypertensive patients usually undergo. Among the strengths of the study was the choice of the setting. Observational studies in primary care, which include typical patient groups and reflect current treatment approaches, are useful to complement the findings of randomized controlled trials[29].

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